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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/517,869 | 10/12/2005 | Anders Lehmann | 5999-0517PUS1 | 3025 |

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| EXAMINER | |
|---|---|
| SPIVACK, PHYLLIS G | |

| ART UNIT | PAPER NUMBER |
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| 1614 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/517,869 | LEHMANN ET AL. | |
| | Examiner | Art Unit | |
| | Phyllis G. Spivack | 1614 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *18 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *15-28* is/are pending in the application.

4a) Of the above claim(s) *26,27 and 1923* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-18,24,25 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/6-04; 6-28-07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

A Preliminary Amendment filed December 16, 2004 is acknowledged. Claims 1-14 are canceled, and new claims 15-28 are presented.

In response to a Restriction Requirement, Applicants elected Group I, drawn to methods for inhibiting transient lower esophageal sphincter relaxations (TLESRs), for the treatment of GERD, for the prevention of reflux, for the treatment or prevention of regurgitation comprising administering a metabotropic glutamate receptor 5 antagonist. Further, Applicants elected the single species 2-methyl-6-(phenylethynyl)-pyridine (MPEP). Both elections were made with traverse.

The traversals are on the grounds that in Applicants view, the present application relates to a single general inventive concept by reciting a corresponding special technical feature, i.e., the use of an effective amount of a metabotropic glutamate receptor 5 (mGluR5) antagonist, regardless of whether or not different organ systems are encompassed by the present claims.

The prior art teaches metabotropic glutamate receptors have ubiquitous effects. In addition to mediating glutamatergic synaptic transmission by acting at ionotropic receptors, glutamate also activates a family of G-protein-coupled receptors that modulate neuronal excitability and synaptic transmission. See Martin et al., Neurogastroenterology & Motility Conference (2001). Further, in view of the sensitivity or specificity of said receptors, and the various functionalities encompassed among those compounds that are deemed to be metabotropic glutamate receptor 5 (mGluR5) antagonists, an undue search burden is presented to the Examiner.

Applicants' argument has been given careful consideration but is not found persuasive.

The Restriction Requirement and Election of Species Requirement are still deemed proper and are adhered to. The Requirements are hereby made FINAL.

Accordingly, the subject matter initially under consideration are those methods of treatment drawn to inhibiting transient lower esophageal sphincter relaxations (TLESRs), treating GERD, preventing reflux, treating or preventing regurgitation comprising administering the metabotropic glutamate receptor 5 antagonist, 2-methyl-6-(phenylethynyl)-pyridine (MPEP), claims 15-18, 24, 25 and 28.

Those methods drawn to other treatments, as well as the administration of metabotropic glutamate receptor 5 antagonists other than 2-methyl-6-(phenylethynyl)-pyridine, claims 19-23, 26 and 27, are presently withdrawn from consideration by the Examiner, as drawn to non-elected inventions, 37 CFR 1.142(b). Re-affirmation of the elections is requested when Applicants respond to this Office Action.

Information Disclosure Statements (IDS) filed December 16, 2004 and June 28, 2007 are further acknowledged and have been reviewed. All of the cited references in the first IDS are encompassed in the second filing.

Claims 17, 18, 24, 25 and 28 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention. The claims are directed to the prevention of reflux and the prevention of regurgitation. The specification provides no support for prevention of these conditions. The metabotropic glutamate receptor 5 antagonists MPEP and 3-fluoro-5-[3-(5-fluoropyridin-2-yl)-1,

2, 4-oxadiazol-5-yl]benzonitrile, disclosed in Examples 1-3, pages 10-13 of the specification, are shown to inhibit lower esophageal sphincter relaxations by a percentage.

Attention is directed to *In re Wands*, 8 USPQ2d 1400 where the court set forth factors to consider when assessing whether or not a disclosure would require undue experimentation. These factors are:

1) the quantity of experimentation necessary

2) the amount of direction or guidance provided

3) the presence or absence of working examples

4) the nature of the invention

5) the state of the art

6) the relative skill of those in the art

7) the predictability of the art and

8) the breadth of the claims.

The instant specification fails to provide guidance that would allow the skilled artisan background sufficient to practice the instant invention without resorting to undue experimentation in view of further discussion below.

The nature of the invention, state of the prior art, relative skill of those in the art and the predictability of the art

The claimed invention relates to therapeutic modalities for pathologies of the lower esophageal sphincter. The recited species that are characterized as metabotropic glutamate receptor 5 antagonists are MPEP and 3-fluoro-5-[3-(5-fluoropyridin-2-yl)-1, 2, 4-oxadiazol-5-yl]benzonitrile. These individual compounds are structurally distinct. Therefore, it would have

been reasonable to expect their diverse functionalities would impart different chemical and physical properties. Although Martin et al. (cited *supra*) suggest a therapeutic application to treatment of GERD, the prior art collectively fails to recognize an effect on the gastrointestinal system.

The relative skill of those in the art is generally that of a Ph.D. or M.D. with expertise in the area of gastroenterology.

The term "prevent" is an absolute definition that means to stop from occurring and thus requires a higher standard for enablement than does "therapeutic" or "treat". It is well established in the medical arts that the vast majority of diseases suffered by mankind cannot be totally prevented with current therapies.

The breadth of the claims

The claims are very broad in terms of the structurally diverse compounds encompassed in the language of the claims.

The amount of direction or guidance provided and the presence or absence of working examples

The working examples are limited to the administration of two metabotropic glutamate receptor 5 antagonists. No guidance is provided to prevent either reflux or regurgitation.

The quantity of experimentation necessary

Applicants have failed to provide guidance as to which particular compound would be preferred for preventing reflux or preventing regurgitation comprising administering a metabotropic glutamate receptor 5 antagonist. The skilled artisan would expect the interaction of a particular compound in a therapeutic regimen to be very specific and highly unpredictable

absent a clear understanding of the structural and biochemical basis for each agent. The instant specification sets forth no such understanding. The characterization of a particular compound as a metabotropic glutamate receptor 5 antagonist does not presage efficacy for preventing reflux or preventing regurgitation in view of the diverse functionalities of the compounds of the instant claims. Absent reasonable *a priori* expectations of success for using any particular agent characterized as a metabotropic glutamate receptor 5 antagonist based solely on receptor affinity, one skilled in the gastroenterology art would have to test extensively many compounds to discover which proves efficacious for preventing reflux or treating or preventing regurgitation. Since each prospective embodiment, as well as future embodiments as the art progresses, would have to be empirically tested, undue experimentation would be required to practice the invention as it is claimed in its current scope. The specification provides inadequate guidance to do otherwise.

Considering the state of the art, which does not recognize metabotropic glutamate receptor 5 antagonist for use in the treatment of the recited preventative methods of use, the high unpredictability of prevention and the lack of guidance provided by the specification, one of ordinary skill in the gastroenterology art would be burdened with undue experimentation.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-18, 24, 25 and 28 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. In the instant case, the claims recite inhibiting transient lower esophageal sphincter relaxations (TLESRs), treating GERD, preventing reflux, treating or preventing regurgitation comprising administering the metabotropic glutamate receptor 5 antagonist. Passages from The Merck Index are provided to show various and unrelated etiologic factors that may cause or be the result of TLESRs. Most fundamentally, GERD is the result of incompetence of the lower esophageal sphincter. However, variations in intrinsic sphincter pressure, the presence or absence of an inflammatory process, the angle of the cardioesophageal junction, the action of the diaphragm, the effect of gravity, the volume of gastric contents, local mucosal protective functions and the general health status of the patient must be considered. It is unclear whether or not functional vomiting is encompassed in the present claim language. As required by instant claim 18, a nexus between inhibition of TLESRs and a condition of passively spitting up gastric contents is absent. Further, it is unclear whether conditions of psychogenic vomiting and a correlation to inhibition of TLESRs are contemplated by the present claim language. There is insufficient written basis for the subject matter of claims 15-18, 24, 25 and 28. This is a Written Description rejection.

M.P.E.P. § 2163 states, "An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention...one

must define a compound by 'whatever characteristics sufficiently distinguish it'. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process."

While the Tables on page 11 demonstrate a percent inhibition of TLESRs in an animal model, there is inadequate written disclosure directed to various pathologies that are characterized by "reflux," that may or may not be of a gastroesophageal origin, "regurgitation," that may or may not be limited to a pediatric population, and transient lower esophageal sphincter relaxations, which the prior art recognizes as caused by unrelated, or etiologically distinct, factors. Applicants have not conveyed possession of the invention with reasonable clarity to one skilled in the art, particularly with respect to dosing regimens that would be required as, particularly, in the case of regurgitation in an infant, or in the case of psychogenic vomiting. The disclosure lacks sufficient written description for all claimed limitations. No working examples are provided that would describe to one of ordinary skill in the art an embodiment that meets all the limitations of the claims. Sufficient guidance to support predictable operability of the invention to one of ordinary skill in the art is absent.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Phyllis G. Spivack whose telephone number is 571-272-0585. The Examiner can normally be reached on 10:30 AM-7 PM.

If attempts to reach the Examiner by telephone are unsuccessful after one business day, the Examiner's supervisor, Ardin Marschel, can be reached on 591-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phyllis G. Spivack
Primary Examiner
Art Unit 1614

Phyllis Spivack

PHYLLIS SPIVACK
PRIMARY EXAMINER

July 7, 2007